REMARKS

The claims have been amended to address the examiner's concerns having regard to question of groups forming a methylene unit and to remove certain conditions from the definition of what may be treated by the compounds specified. To facilitate further prosecution, the nature of the substitution in the pyranone ring in claim 1 has been simplified X2 and T in the Formule I, and "R1 and R2 are each independently Y and [CH_2CH (OH) CH_2]Y" have been deleted. As a result of changes in Formula 1, appropriate revisions have also been made. Alkenyl and alkynyl have been deleted across the claims.

The nature of the rejection under 35 USC 112 first paragraph is not entirely clear. Reference is made to the breadth of the claims and the number of conditions referred to but only two specific points are made: the definition of Y and the reference to various groups combining to form a methylene group.

So far as the question of the breadth of the definition of the compounds in claim 1 is concerned, it is submitted that as amended one skilled in the art would recognize that the compounds specified would have similar properties. All require an aryl-substiuted chromone nucleus with three oxygen-linked substituents to one of the chromone rings. Claim 1 has been amended to limit the claims to methods of using a more tightly defined group of compounds. It is noted that the examiner did not raise any objection to the scope of the definition of the compounds of use set out in claims 31 and 60 wherein the nature of the compounds is already tightly defined.

So far as the conditions to be treated are concerned, these have been limited to conditions arising from overproduction of TNF-a, overproduction of superoxide anion radical, organ damage to liver kidneys or lungs. It is submitted that the specification is enabling for treatment of these conditions. Those skilled in the art have an understanding of the nature of these conditions. Submitted herewith is a brief literature survey provided by the assignee of the present application on the nature of diseases associated with overproduction of TNF-α and of reactive oxygen species such as superoxide. The teaching of the present

application should be read against this background. The specification provides data showing the effect of baicalein-6-sulfate in tests relating to TNF-α inhibition, superoxide anion production, liver enzyme function (SGPT and SGOT which are indicative of the effects on damage livers) and histological studies showing the effect on lung tisue in LPS-treated rats and the effect of baicalein on TNF-α. and superoxide in LPS-treated rats. Additional data are submitted herewith showing TNF-α inhibition for several additional compounds falling within the claims. The application itself provides data for R_1, and R_3 as methyl, R_2 as sulfate, sodium salt, X_1 as phenyl and X_2 as hydrogen. The additional data submitted herewith include data for compounds wherein R1 is hydrogen or methyl, R_2 is hydrogen or methyl, R_3 is hydrogen, methyl, or sulfate, sodium salt, X_1 is phenyl, 4'-aminophenyl, 4'-(hydroxyl)phenyl, 4'-(2-hydroxyethoxy)phenyl, 4'-(2-aminoethyl)phenyl and X_2 is hydrogen or phenyl. It is therefore submitted that the claims are enabled by the description throughout there scope both having regard to the nature of the compounds used and the conditions that are specified as being treated.

So far as the particular points made by the examiner are concerned, the definition of Y is a narrow one and clearly set out in the application as originally filed. The basis for the examiner's rejection is therefore not understood.

So far as the groups combining to form methylene is concerned, the language has been revised at all locations to make it clear that the group formed is a five-membered ring comprising a methylene dioxy linkage.. The original specification referred to the groups in question in the terms of one option being that they "together are heterocycles". The last two compounds whose preparation is described on page 35 of the specification are compounds wherein the substitents in the 6 and 7 positions (i.e. R^1 and R^2) form part of a methylene dioxy group. Such disclosure provides guidance as to the meaning of the term "together are heterocycles" and defines the simplest structure that could meet the requirement. It is therefore submitted that the application provides adequate support for the revised language now used to replace "together are heterocycles" at all points where such language was originally used in the claims.

It is therefore submitted that the requirements of 35 USC 112 have been met.

Turning now to the art-based rejections, it is noted that these have been raised only against the compound per se and pharmaceutical composition claims and not against any of the method of treatment claims.

Cassels describes compounds having anxiolytic properties covering a variety of flavone derivatives in which the 5, 6, 7, 8 and 4' positions are preferably hydrogen, hydroxyl or halo and the most particularly preferred are those wherein the 5 substituent is hydroxyl or hydrogen, the 6-substituent halo, the 7-substituent hydroxyl or halo, the 8-substituemnt halo and the phenyl group is substituted by hydroxyl. Specific named preferred compounds are:

Compound	Substituent position				
	5	6	7	8	Phenyl substituent
Flavone	H	H	H	H	H
Chrysin	OH	H	OH	H	H
Apigenin	OH	H	OH	H	4-OH
2'-chlorochrysin	OH	H	OH	H	2-Cl
2'-fluorochrysin	OH	H	OH	H	2-F
6,8-dibromochrysin	OH	Br	OH	Br	H
7-bromo-flavone	H	H	Br	H	H

All of these lack an oxy link in the 6 position which is an essential feature of the applicant's claims.

No mode of action for the anxiolytic effects is indicated and there seems no reason to suppose that compounds having anxiolytic effects would have any effect on treatment of organ damage. There is therefore no reason why one skilled in the art would seek to modify the compounds described to produce compounds having the structure and properties of the compounds of the present claims.

Handler relates to derivatives of isoflavones wherein X1 of the present claims is hydrogen and X2 phenyl or substituted phenyl. Most of the specific compounds referred to have glucose substituents and the compounds of the present invention are distinguished from such references for this reason. Compounds lacking a glucose substituent that can form the base of

the claimed derivatives are

	5	6	7	8	4'
Glycetein	H	OMe	OH	H	H
Genistein	OH	H	OH	H	OH
Daidzein	H	H	OH	H	OH

Again lack of an oxy-linkage in all of the 5, 6, and 7 positions distinguishes these compounds from those of the present invention.

The purpose of Handler's invention is to produce ester derivatives that are of enhanced aqueous solubility by esterifying one of the 5, 6, 7 or 4' positions with a carboxylate or phosphate ester group. The suggested uses include anti-cancer activity and inhibition of tyrosine kinase. Other suggested activities include antiangiogenic, antihemolytic, antiischemic, antileukemic, antimitogenic, antimutagenic, antioxidant, fungicidal, pesticidal, MAO-inhibition, phytoalexin. Again, there is no reason to believe that compounds having any such properties would be useful to treat organ damage Or any other reason to modify them to produce compounds falling within the scope of the present claims.

Lee describes the use of a wide range of flavones to inhibit expression of inducible nitric oxide synthase (iNOS) or cyclooxygenase-2 (COX-2), activating K^+ channels, treating septic shock, preventing aneurism, inhibiting angiotensin converting enzyme and reducing inflammation. No mortality data nor reduction of cardiovascular crisis in animals, two parameters used clinically to judge treatment effects in septic shock, were done to support treating septic shock. They did not have animal models in the application, nor they claim sepsis in US patent (US 6,806,257). LPS is a common biological toxin isolated from commonly isolated from E. coli, originally used for septic shock animal models and nowadays used as a laboratory tool to study for various immunological events. No mention is made of treating organ damage or diseases or conditions associated with over-production of TNFα or with over-production of superoxide. The preferred flavones are:

	5	6	7	8	Phenyl substituent
Oroxylin A	OH	OCH_3	OH	H	H

Wogonin OH H OH OCH_3 H

Wogonin does not lie within the scope of applicants defined compounds because of the presence of a methoxy group in the 8 position.

The compounds of the present invention all have an oxygen linking in each of the 5, 6 and 7 positions and are unsubstituted in 8 position. Additionally when X^1 is substituted phenyl, they preferably have a hydroxyl or amino-containing group in the 4' position.

So far as the broad general disclosures of the prior art are concerned, it is pointed out that the compounds claimed in the present application fall in a genus-species relationship with each of the prior art references. Thus we must look to the Guidelines set out at MPEP 2144.08. According to the Guidelines, the question to be decided in species-genus situations is whether the prior teaching provided any reason to produce what is now being claimed. Such consideration requires looking at predictability in the particular art, the properties of the species as compared to those taught for the prior genus and the closeness in structure of the claimed species to typical or preferred species taught in the prior generic disclosure. It is submitted that in the present case, as now amended, the claims are of sufficiently different structure from any specific compound set out in the prior art references and have properties differing from those described in the prior art that there is no reason to modify any of the compounds described in the prior art to produce the compounds claimed. In order to find a new compound obvious over a broad general prior art teaching, it is necessary to have a reason to choose a particular starting material as a point from which to commence modification and also to have a reason to make the specific modification that was effected by the applicant. **Takeda Chemical Industries v. Alphapharm Pty. Ltd.** 83 USPQ2d 1169 (Fed. Cir. 2007) and **Eisai Co. Ltd. v. Dr Reddy's Laboratories Ltd.** 87 USPQ2d 1452 (Fed. Cir. 2008). There is no reason for taking either of these steps in the present case

Of the specific compounds noted above, oroxylin A falls within the definition of Claim 1 as previously presented and Claim 1 has been amended to limit the definition of the 6-

substituent to hydroxy, sulfate and phosphate. There is no reason why one skilled in the art would have thought to modify oroxylin A to produce a compound as now claimed. . As noted by the Supreme Court in *KSR International Co. v. Teleflex, Inc.* 550 U.S. 398 82 USPQ2d 1385 (2007) .

> [R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

There is no rational underpinning for modification of this compound to produce one within the scope of the amended claims.

It is therefore submitted that all claims now meet the requirements of 35 USC 102 and 103.

In view of the foregoing, it is submitted that this application is in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

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Protocol of TNFα inhibition assay

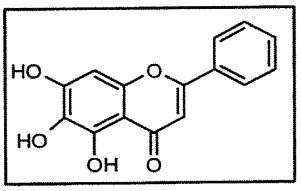
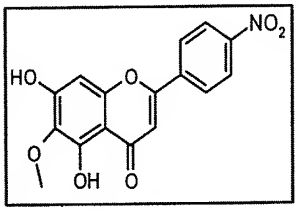
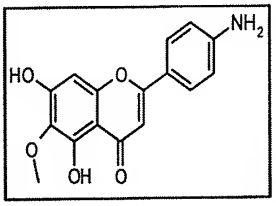
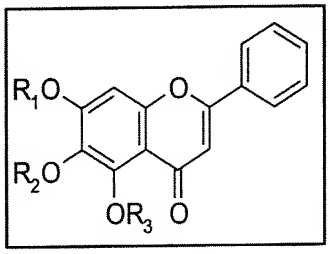
1. **MTT assay** is used to evaluate the cell viability. The MTT>70% of vehicle control is assumed that the drug shows no cell toxicity at indicated drug concentration.

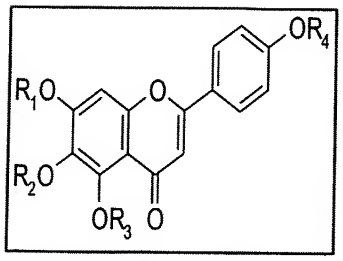
MTT: 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide.

2. Protocol of TNFα inhibition assay

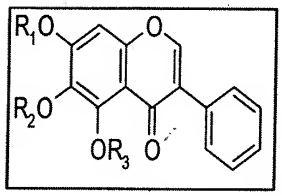
After stimulated U937 cells with 50 ng/ml PMA for 24 hrs, cells were cultured with fresh medium for further 48 hrs. Adherent cells were scraped off and resuspended in fresh medium. U937 cells in 100 μl culture medium were mixed with 80 μl of fresh medium and 10 μl various concentration of test drug in each well of 96-well microculture plate. After 30 minutes agitation, cells were stimulated with 0.1 μg/ml LPS at 37°C for 4 hrs except for the negative control. Culture medium (120 μl) was then collected for determining the amount of TNFα production with ELISA (R&D systems). The 50% inhibitory concentration (IC50) of each drug on TNFα production was calculated with software GraFit. TNFα 100% production was presented in cells treated with vehicle and stimulated with LPS . The viability of cells was determined by incubation with 100 μl of 1 mg/ml MTT reagent in each well, and the optical density values obtained were compared with negative control, which treated with vehicle without LPS stimulation.

In vitro Inhibition of LPS induced TNF-a release in U937 Cells

	TNF-a (in vitro) Inhibiiton EC50 or % of Inhibition at uM
Baicalein 	**31% at 100 uM**
	**no activity at 100 uM**
	**69±25 uM**
 R1 = R2 = R3 = CH3 R1 = R2 = R3 = H R1 = CH3 , R2 = R3 = H R1 = R3 = H, R3 = SO3Na	**18% at 100 uM**



R1 = R2 = R3 = R4 = H	**78±23 uM**
R1 = R2 = R3 = CH3 , R4 = H	NA
R1 = R2 = R3 = R4 = CH3	NA
R1 = R2 = R3 = CH3 , R4 = CH2Ph	NA
R1 = R2 = R3 = CH3 , R4 = CH2CH2OH	**14% at 33 uM**
R1 = R2 = R3 = CH3 , R4 = CH2CH2CH2OH	NA
R1 = R2 = R3 = CH3 , R4 = CH2CO2CH3	NA
R1 = CH3 , R2 = R3 = R4 = H	NA
R1 = R2 = R3 = CH3 , R4 = CH2CH2NH2	**32% at 100 uM**
R1 = R2 = R3 = CH3 , R4 = CH2CH2CH2NH2	NA



R1 = R2 = R3 = H	**20% at 100 uM**
R1 = R2 = R3 = CH3	NA
R1 = R2 = CH3, R3 = H	NA
R1 = R3 = H, R2 = CH3	NA
R1 = CH3, R2 = R3 = H	NA

NA = not available or tested